ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 1998, p. 3086–3091 Vol. 42, No. 12
0066-4804/98/$04.00+0

Ambulatory Treatment of Multidrug-Resistant *Staphylococcus*-Infected Orthopedic Implants with High-Dose Oral Co-trimoxazole (Trimethoprim-Sulfamethoxazole)

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Received 29 January 1998/Returned for modification 13 April 1998/Accepted 22 September 1998

We examined the effectiveness and safety of high-dose oral co-trimoxazole (trimethoprim-sulfamethoxazole) for the treatment of orthopedic implants infected with multidrug-resistant *Staphylococcus* species. The prospective study was conducted between 1989 and 1997 in a university medical center with ambulatory-care services. Patients eligible for the study consisted of those from whom multidrug-resistant *Staphylococcus* spp. organisms susceptible only to glycopeptides and co-trimoxazole were isolated from their orthopedic implants and for whom there was no contraindication to the treatment. All patients were treated orally with high-dose co-trimoxazole (trimethoprim, 20 mg/kg of body weight/day; sulfamethoxazole, 100 mg/kg/day). Patients with prosthetic hip infections were treated for 6 months, with removal of any unstable prosthesis after 5 months of treatment; patients with prosthetic knee infections were treated for 9 months, with removal of any unstable prosthesis after 6 months of treatment; and patients with infected osteosynthetic devices were treated for 6 months, with removal of the device after 3 months of treatment, if necessary. Monthly clinical evaluations were conducted until the completion of the treatment, and follow-up examinations were conducted regularly for up to 6 years. The overall treatment success rate was 66.7% (26 of 39 patients), with success rates of 62.5% for patients with prosthetic knee infections, 50% for those with prosthetic hip infections, and 78.9% for those with other device infections. Seventeen of the 28 (60.7%) patients who did not have any orthopedic material removed were cured. Eight patients stopped the treatment because of side effects, and one patient was not compliant. In three patients treatment failed because of the appearance of a resistant bacterium. Long-term oral ambulatory treatment with co-trimoxazole appears to be an effective alternative to the conventional medicosurgical treatment of chronic multidrug-resistant *Staphylococcus*-infected orthopedic implants which includes long-term intravenous antibiotic therapy combined with surgical debridement and removal of foreign material or its subsequent one- or two-stage replacement.

Chronic bone and joint infections are some of the most difficult infections to manage. Even aggressive medicosurgical treatments are not always able to guarantee permanent eradication of the infectious process, particularly when these infections occur in patients with foreign orthopedic material. Most of these infections are nosocomially acquired, and reported infection rates following hip arthroplasty vary from 0.5 to 1% (28, 31) and are 1 to 2% following knee arthroplasty (16, 28). The increase in the number of hip and knee replacements over the past 10 years in developed countries has resulted in an increase in the overall number of infected patients, despite a reduction in the infection rate. Coagulase-positive and coagulase-negative staphylococci account for 45 to 55% of these infections, regardless of the type of implant (2, 3, 17). The staphylococci isolated from these patients are mostly always oxacillin resistant (33). Conventional treatment of these infections includes long-term intravenous antibiotic therapy, in combination with surgical debridement and removal of the orthopedic material or, if possible, its one- or two-stage replacement (3, 11, 20, 36, 37).

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Over the last few years the use of oral, long-term ambulatory antibiotic treatment such as rifampin combined with either fluoroquinolones or fusidic acid has been proposed as an alternative approach to the treatment of these chronic infections. The effectiveness and safety of oral ofloxacin combined with rifampin for the treatment of these infections have been reported previously (9), with an overall success rate of 74%. Unfortunately, over the last few years quinolone resistance has dramatically increased, particularly in hospital-acquired infections. In a recent study with a limited number of patients (8), we recommended the association of oral fusidic acid plus rifampin for the treatment of infected orthopedic implants when quinolone-resistant staphylococci were implicated. However, when staphylococci are resistant to all the antibiotics listed above, glycopeptides (vancomycin and teicoplanin) and co-trimoxazole (trimethoprim-sulfamethoxazole) are generally the only agents that remain active in vitro and that are able to diffuse into bone and joint tissues (39). We evaluated the feasibility of using oral co-trimoxazole as an alternative to the long-term parenteral administration of glycopeptides in the ambulatory treatment of multidrug-resistant *Staphylococcus*-infected orthopedic implants. The low concentration of co-trimoxazole in the bone tissue in contact with the foreign material led to a decision to increase the dose usually prescribed for bacterial infections (26) to a higher level such as that used in the management of AIDS patients with parasitic

infections, e.g., *Pneumocystis carinii* pneumonia or cerebral toxoplasmosis (trimethoprim, 20 mg/kg of body weight per day; sulfamethoxazole, 100 mg/kg of body weight per day) (30, 34).

In this paper we report on the results of a study of oral ambulatory treatment with high-dose co-trimoxazole of 39 patients with multidrug-resistant *Staphylococcus*-infected orthopedic implants among the 380 patients with chronic osteoarticular infections treated in our department between 1989 and 1997.

MATERIALS AND METHODS

Patients. Thirty-nine patients with infected orthopedic implants were included in this study. A patient was included in the study when all of the following criteria were met. (i) The patient had clinical, biological, and radiological evidence of an orthopedic implant infection (orthopedic implants included protheses, plates, and intramedullary nails). Evidence of an orthopedic device infection was established by the presence of at least one of the following: productive fistula, pain and biological inflammatory syndrome, radiological evidence of device looseness and biological inflammatory syndrome, or joint swelling and biological inflammatory syndrome. Biological inflammatory syndrome was manifested by an erythrocyte sedimentation rate greater than 50 mm/h and an elevated level of C-reactive protein. If present, extension of the fistula to the orthopedic material was confirmed by fistulography with a radiographic contrast agent. (ii) Leukocytes and gram-positive cocci had to be present upon direct examination of pus samples; and the same *Staphylococcus* species, as determined by biotyping and antibiotic susceptibility testing, had to be isolated at least three times on 3 different days from the discharge of the fistula or at least once from a joint aspirate or a surgical bone biopsy specimen. (iii) The *Staphylococcus* isolate had to be resistant in vitro to all antistaphylococcal antibiotics except co-trimoxazole and glycopeptides (vancomycin and teicoplanin), with no alternative antimicrobial therapy except glycopeptides permitted. (iv) The patient could have no contraindication to the use of co-trimoxazole, and patient was required to have normal renal and hepatic functions. (v) The patient could not be receiving any other antibiotic regimen for the treatment of the infected orthopedic implant. (vi) The patient had to be available for a follow-up period of at least 24 months after the completion of treatment. (vii) Informed consent had to be obtained from the patient.

All eligible patients were included in the study; and at the time of inclusion, demographic, clinical, laboratory (including full blood and differential counts, hepatic enzyme levels, erythrocyte sedimentation rate, and C-reactive protein levels), and radiological data were recorded.

Sample collection and bacterial culture. When possible, pus was sampled with a compress or a swab; otherwise, pus was sampled by needle aspiration of the prosthesis or by surgical biopsy when three consecutive aspirations remained sterile. Direct microscopic examination of the pus after Gram staining was performed to date the presence of polymorphonuclear leukocytes and bacteria. The bacterial isolation procedure has been described previously (38). Briefly, in parallel with conventional isolation procedures, we used a lysis-centrifugation method which consisted of rapid freezing of the clinical samples in liquid nitrogen followed by thawing at 37°C. The freeze-thaw step was repeated twice, and the sample was then inoculated as described above for the standard procedure. Identification of the bacteria and antibiotic susceptibility tests were performed by using AutoSCAN-W/A (Dade International, West Sacramento, Calif.), and if necessary, the results were confirmed by conventional methods with the API (Montalieu-Vercieu, France) system for the identification of bacteria and the agar diffusion method for antibiotic susceptibility tests (the following antibiotics were tested: oxacillin, erythromycin, pristinamycin, gentamicin, ofloxacin, ciprofloxacin, fusidic acid, rifampin, teicoplanin, vancomycin, and trimethoprim-sulfamethoxazole).

Treatment protocol. Co-trimoxazole (trimethoprim, 10 mg/kg of body weight; sulfamethoxazole, 50 mg/kg of body weight) was administered orally twice a day. The overall design of the treatment protocol was dictated by the type of infection. (i) For patients with prosthetic hip infections, antibiotics were administered orally for a total of 6 months. For patients with an unstable prosthesis, one-stage removal and reimplantation of the hip prosthesis was performed after 5 months of antibiotic treatment; for other patients the prosthetic material was conserved. (ii) For patients with prosthetic knee infections, antibiotics were administered orally for a total of 9 months. For patients with an unstable prosthesis, one-stage removal and reimplantation of the knee prosthesis was performed after 6 months of antibiotic treatment; for other patients the prosthetic material was conserved. (iii) For patients with osteosynthetic device infections, antibiotics were administered orally for 6 months, with the foreign body being removed after 3 months of therapy if necessary.

Follow-up. During the 6- or 9-month antibiotic treatment period, monthly clinical examinations (including questions about the use of analgesics or nonsteroidal medications, pain and signs of dysfunction, and physical examination) and laboratory analyses (including blood and differential counts, erythrocyte sedimentation rate, C-reactive protein level, blood biochemistry, creatinine clearance, and hepatic enzyme levels) were performed. After the completion of therapy, the patients underwent the same clinical and biological evaluations and radiological follow-up at months 3, 6, 12, 18, 24, 36, 48, 60, and 72. Antibiotic treatment was stopped when no clinical, biological, or radiological evidence of infection was present following the completion of the treatment protocol or at any time during a documented treatment failure.

In the case of treatment failure, the evaluation procedure included the following: verification of the patient's compliance including determination of antibiotic concentrations in the purulent drainage from the fistula and in the patient's urine (38), conventional radiography and fistulography, and a bacteriological evaluation. When bacteria were cultured, identification and biotype indicated by the AutoSCAN-W/A and antibiotic susceptibility patterns of the organisms isolated from a patient at the time of treatment failure were compared with those of the organisms isolated at the time of diagnosis. Cure was defined as the absence of clinical, biological, and radiological evidence of infection after the completion of treatment; treatment failure was defined as the absence of cure; and relapse was defined as the reappearance of infection due to the same *Staphylococcus* isolate that caused the original infection, regardless of the timing of this secondary infection.

Reported follow-up durations date from the end of treatment, and only the results for patients with a follow-up of at least 24 months are included in this paper.

RESULTS

In total, 39 patients who had clinical, biological, and radiological evidence of an orthopedic device infection and who fulfilled the case definition were included in the study, which was conducted between May 1989 and May 1997. These patients represented 10.3% of the 380 patients who were treated for a chronic osteoarticular infection over the same time period in our department.

Fistulas were present in 22 (56%) of the 39 patients in the study. *Staphylococcus* species were isolated from the purulent fistulous discharge for 22 (56%) of the 39 patients, after puncture of the infected site for 10 (26%) of the 39 patients, and after surgical biopsy of the infected site for 7 (18%) of the 39 patients. The time delay between the surgical implantation of the orthopedic device and the confirmed microbiological diagnosis of infection ranged from 1 to 70 months. This time delay was less than 3 months for 18 (20.5%) of the 57 patients and more than 12 months for 12 (28.2%) of the 57 patients.

The 39 intention-to-treat patients included 8 with knee prosthesis infections (Table 1), 12 with hip prosthesis infections (Table 2), and 19 with osteosynthetic device infections (Table 3). This group contained 35 males and 14 females and had a median age of 48.7 years (range, 22 to 79 years). Treatment success rates were determined after a posttreatment follow-up of 24 to 75 months (average, 38 months). The overall treatment success rate was 66.7% (26 of 39 patients), with success rates of 62.5% (5 of 8 patients) for patients with prosthetic knee infections, 50% (6 of 12 patients) for patients with prosthetic hip infections, and 78.9% (15 of 19 patients) for patients with other device infections (Table 4). Seventeen of the 28 (60.7%) patients from whom no orthopedic material was removed were cured. Eleven (36.6%) patients needed to have the orthopedic material removed; 9 (81.8%) of these patients were completely cured. Seventeen (65.4%) of the 26 cured patients could be treated by an antibiotic regimen alone. Seven (77.7%) of nine patients who did not respond to a previous antibiotic protocol (ofloxacin plus rifampin for five patients and fusidic acid plus rifampin for four patients) were cured. Among the 39 intention-to-treat patients, 5 (patients 2, 14, 15, 18, and 39) ceased treatment after developing major skin allergies, 3 (patients 21, 22, and 34) ceased treatment because of serious gastrointestinal side effects, and 1 (patient 12) was not compliant. The success rate for the remaining 30 patients who were able to finish the treatment protocol was 86.7% (26 of 30 patients), with success rates of 71.4% (5 of 7 patients) for patients with prosthetic knee infections, 75% (6 of 8 patients) for patients with prosthetic hip infections, and 100% (15 of 15 patients) for patients with other device infections.

TABLE 1. Characteristics of and outcomes for eight patients with staphylococcal infections of their knee prostheses[a]

Patient no.	Sex	Age (yr)	Time delay to infection (mo)	Clinical presentation	Microorganism	Diagnostic procedure	Previous treatment	Prosthesis removal	Outcome	Duration of follow-up (mo)
1	M	75	38	P, L, Fi	CoNS	Fistula		Yes	Cure	40
2	M	71	14	P, I	CoNS	Biopsy	O/R	No	Intolerance	
3	F	69	7	P, I, Fe	CoNS	Puncture		No	Failure	
4	M	76	4	P, I	SA	Puncture		No	Cure	50
5	M	79	20	Fi	SA	Fistula		No	Cure	53
6	F	68	3	P, I, Fe	SA	Puncture		No	Cure	48
7	M	37	27	P, L	CoNS	Puncture		Yes	Failure	
8	F	72	3	Fi	SA	Fistula		No	Cure	43

[a] Abbreviations: SA, *S. aureus*; CoNS, coagulase-negative *Staphylococcus*; M, male; F, female; P, pain; Fe, fever; Fi, fistula; L, loosened prosthesis; I, inflammatory syndrome; O/R, ofloxacin plus rifampin; F/R, fusidic acid plus rifampin.

As for pathogens, 16 (66.7%) of 24 patients with *Staphylococcus aureus* infections were cured, as were 10 (66.7%) of 15 patients with coagulase-negative staphylococcal infections. Three treatment failures (patients 3, 7, and 16) were related to the isolation of a new co-trimoxazole-resistant *Staphylococcus* strain, and one patient (patient 20) had a relapse caused by a *Staphylococcus* strain which remained sensitive to the study drug.

DISCUSSION

Deep infection of foreign-body implants is a common complication found in orthopedic surgery, along with mechanical dysfunction and thromboembolic disease. It can have extreme social repercussions for the patient and an important economic impact on the community because of the long periods of time that the patient must remain in a hospital and in an invalid state. The most common infectious agents are *S. aureus* and coagulase-negative staphylococci, which are encountered in more than 50% of the patients (3, 8, 9, 17). Rigorous application of prophylactic methods (antibiotic prophylaxis, antibiotic-coated cement, sterile operating room environment) has resulted in a fall in the infection rate to less than 2% among patients undergoing nontraumatic surgery (3, 18, 21, 25), but the remaining infections, due to nosocomially acquired and often multidrug-resistant bacteria, are extremely difficult to manage. Simple surgical drainage (with retention of the prosthesis) with nonstandardized antibiotic therapy has had a success rate of only 20 to 30% (1, 12). However, standard antibiotic protocols alone have failed to cure these infections because of periprosthetic microbial adhesion and the existence of an immunoincompetent fibroinflammatory zone around the foreign body (6, 15, 22, 39). The usual treatment of this type of infection requires the removal of the foreign body, followed by an immediate or a delayed arthroplasty exchange (one- or two-stage surgery). Surgical management is associated with intravenous antibiotic treatment for several weeks or months (3, 5, 11, 19–21, 29, 36, 37).

The availability of new fluoroquinolones with good tissue diffusion and with an antibacterial spectrum that includes most bacteria found in orthopedic implant infections prompted trials of oral antimicrobial combinations for their treatment. We previously reported on the feasibility of using the oral combination of rifampin plus ofloxacin for the treatment of staphylococcus-infected orthopedic implants (9). Cure rates were comparable to those obtained by conventional therapy, and in most cases this prolonged antibiotic regimen allowed long-term cure of the infection without implant removal. These results explain why rifampin plus ofloxacin remained our first-line regimen for the treatment of staphylococcus-infected orthopedic implants. Over the last few years, however, quinolone resistance has increased among nosocomially acquired staphylococcal isolates, and currently, 90% of staphylococcal isolates that are resistant to oxacillin are also resistant to fluoroquinolones (32). Consequently, the use of quinolones as antistaphylococcal drugs has decreased and investigators have since turned their attention to other oral antistaphylococcal antibiotics which might be efficacious. We recently reported on the results of a study of oral fusidic acid combined with oral rifampin for the treatment of staphylococcal infections associated with orthopedic implants (8), in which we achieved success rates similar to those of our previous study in which we

TABLE 2. Characteristics of and outcomes for 12 patients with staphylococcal infections of their hip prostheses[a]

Patient no.	Sex	Age (yr)	Time delay to infection (mo)	Clinical presentation	Microorganism	Diagnostic procedure	Previous treatment	Prosthesis removal	Outcome	Duration of follow-up (mo)
9	M	41	26	Fi, I	CoNS	Fistula	O/R	No	Cure	33
10	F	79	11	P, Fe	CoNS	Biopsy	F/R	No	Cure	24
11	M	63	9	P, I	CoNS	Biopsy	F/R	No	Cure	28
12	F	71	2	P, I, Fe	SA	Puncture		No	Lack of compliance	
13	F	63	22	P, L	CoNS	Puncture	F/R	Yes	Cure	24
14	M	77	14	P, L, Fi	SA	Fistula	O/R	No	Intolerance	
15	M	45	7	P, I, Fe	SA	Puncture		No	Intolerance	
16	M	72	23	P, I	CoNS	Puncture		No	Failure	
17	M	68	1	P, I	SA	Puncture		No	Cure	33
18	M	72	70	P, I, Fe	SA	Biopsy		No	Intolerance	
19	M	44	18	P, L, Fi	SA	Fistula		Yes	Cure	32
20	F	64	4	P, L, Fi	SA	Fistula		Yes	Failure	

[a] Abbreviations: SA, *S. aureus*; CoNS, coagulase-negative *Staphylococcus*; M, male; F, female; P, pain; Fe, fever; Fi, fistula; L, loosened prosthesis; I, inflammatory syndrome; O/R, ofloxacin plus rifampin; F/R, fusidic acid plus rifampin.

TABLE 3. Characteristics of and outcomes for 19 patients with staphylococcal infections of their osteosynthetic devices[a]

Patient no.	Sex	Age (yr)	Time delay to infection (mo)	Clinical presentation	Localization	Type of device	Microorganism	Diagnostic procedure	Previous treatment	Device removal	Outcome	Duration of follow-up (mo)
21	F	22	9	P, Fi, I	Ankle	Pl	CoNS	Fistula		No	Intolerance	
22	M	32	6	Fi, I	Knee	Pl	SA	Fistula		No	Intolerance	
23	F	26	3	P, Fi	Tibia	Pl	SA	Fistula		Yes	Cure	49
24	M	41	7	P, Fe	Tibia	Pl	CoNS	Biopsy		Yes	Cure	39
25	M	23	2	P, Fe, I	Femur	Pl	SA	Biopsy		Yes	Cure	37
26	M	44	10	P, Fi, I	Tibia	IMN	CoNS	Fistula	O/R	No	Cure	45
27	M	47	1	P, Fi	Tibia	Pl	CoNS	Fistula		No	Cure	54
28	F	22	9	P, Fi	Ankle	Pl	SA	Fistula		No	Cure	57
29	M	53	1	Fi	Ankle	Pl	SA	Fistula		No	Cure	75
30	F	58	6	P, Fi, I	Tibia	IMN	CoNS	Fistula	O/R	No	Cure	65
31	M	28	2	P, Fe, I	Tibia	Pl	SA	Biopsy		Yes	Cure	48
32	F	36	4	P, Fi	Ankle	Pl	CoNS	Fistula		No	Cure	52
33	M	35	20	Fi	Tibia	Pl	SA	Fistula	F/R	Yes	Cure	45
34	M	16	7	P, I	Tibia	Pl	SA	Puncture		No	Intolerance	
35	M	50	2	P, Fi, I	Tibia	Pl	SA	Fistula		Yes	Cure	73
36	M	22	1	P, Fe, Fi	Tibia	IMN	SA	Fistula		No	Cure	24
37	F	37	11	Fi	Ankle	Pl	SA	Fistula		No	Cure	49
38	M	43	4	P, Fi	Tibia	Pl	SA	Fistula		No	Cure	25
39	M	29	5	P, Fi, I	Tibia	Pl	SA	Fistula		No	Intolerance	

[a] Abbreviations: SA, *S. aureus*; CoNS, coagulase-negative *Staphylococcus*; M, male; F, female; P, pain; Fe, fever; Fi, fistula; I, inflammatory syndrome; Pl, plate; IMN, intramedullary nail; O/R, ofloxacin plus rifampin; F/R, fusidic acid plus rifampin.

evaluated the effectiveness of oral rifampin plus ofloxacin (9). Nevertheless, in both studies, treatment failures were primarily related to the isolation of resistant staphylococci, stressing the importance of using new antibiotics that are effective against these multidrug-resistant staphylococci. Furthermore, the rates of resistance to the quinolones and fusidic acid among staphylococci have increased dramatically and now average 55 and 45%, respectively, in our hospital. The only antibiotics that remain active against multidrug-resistant staphylococci and that are able to diffuse into bone tissue are glycopeptides (vancomycin and teicoplanin) (10, 14, 27) and co-trimoxazole (26). Although multidrug-resistant staphylococci often remain sensitive in vitro to co-trimoxazole, this antibiotic is considered to be substantially less effective than glycopeptides (24). Both vancomycin and teicoplanin are potentially nephrotoxic and can be administered only by the parenteral route. Use of the parenteral route of drug delivery is not a major inconvenience in the traditional approach in which patients with chronic bone and joint infections are admitted to a hospital for the total duration of medicosurgical therapy. Nowadays, however, in an effort to control escalating costs, patients with chronic infections should be admitted to a hospital only for the initiation of treatment and at around the time of surgical therapy, and when possible, the remainder of therapy should be continued on an outpatient basis (7).

Co-trimoxazole is useful in the treatment of a wide spectrum of bacterial infections. The standard dosage is trimethoprim at 5 mg/kg/day and sulfamethoxazole at 25 mg/kg/day; e.g., two tablets twice a day or one double-strength tablet twice a day. Co-trimoxazole may also be used for the treatment of parasitic infections, e.g., susceptible *Plasmodium falciparum* infections, toxoplasmic encephalitis, and *P. carinii* pneumonia in immunocompromised patients with or without AIDS. In these patients, the usual recommended dose is much higher than the standard regimen; thus, trimethoprim at 20 mg/kg/day and sulfamethoxazole at 100 mg/kg/day are administered in two or three doses orally or intravenously (23, 30, 40). Co-trimoxazole has a high level of in vitro activity against most *Staphylococcus* species (26, 33), and it has been useful in the treatment of acute and chronic osteomyelitis (40). Because we had previously been unable to cure patients with orthopedic implant infections treated with standard doses of co-trimoxazole (unpublished data), we administered the higher doses used for the treatment of parasitic infections in order to increase the antibiotic concentration in the bone tissue and, more particularly, in the zone of contact with the foreign material.

Compared to previous studies dealing with long-term oral antibiotic regimens for the treatment of *Staphylococcus*-infected orthopedic devices (8, 9), we noticed that a relatively high percentage of patients (20.5%) had to cease their regimens because of severe, previously observed (13, 30) side effects (allergic skin manifestation, vomiting, and diarrhea). This

TABLE 4. Cure rate for intention-to-treat patients with infected orthopedic devices[a]

Type of prosthesis	Cure rate (no. of patients cured/no. of patients treated [%]) for patients with the following infections and treatments:				
	SA, antibiotics	SA, antibiotics, device removal	CoNS, antibiotics	CoNS, antibiotics, device removal	Total
Hip	1/5	1/2	3/4	1/1	6/12 (50)
Knee	4/4	0/0	0/2	1/2	5/8 (62.5)
Osteosynthetic	5/8	5/5	4/5	1/1	15/19 (78.9)
Total	10/17	6/7	7/11	3/4	26/39 (66.7)

[a] Abbreviations: SA, *S. aureus*; CoNS, coagulase-negative *Staphylococcus*.

may explain the discrepancy in the cure rate in intention-to-treat patients (66.7%) compared to that in patients who finished the treatment protocol (86.7%). Co-trimoxazole interferes with folic acid metabolism; and megaloblastic anemia, neutropenia, and thrombocytopenia have been described with prolonged use of co-trimoxazole (40). In our study five patients (patients 1, 4, 5, 10, and 17) presented with megaloblastic anemia during the treatment period and were treated with folinic acid; for none of them did the antibiotic regimen need to be interrupted, and all of them were cured. In three patients (patients 3, 7, and 16), treatment failures were related to the isolation of co-trimoxazole-resistant staphylococci. This may be explained by the fact that in some patients the failure to note and to examine different strains of coagulase-negative staphylococci in the original cultures resulted in a lack of complete initial microbiological documentation. In those patients with an initial infection with more than one *Staphylococcus* strain, some bacteria could have been resistant to co-trimoxazole, explaining the treatment failure and the further isolation of staphylococci resistant to this antibiotic. On the other hand, this may indicate that either trimethoprim or sulfamethoxazole did not reach concentrations effective in situ, resulting in some cases in pseudomonotherapy. The overall cure rate of 66.7% was similar not only to those obtained in our previous studies of oral rifampin plus ofloxacin (9) and rifampin plus fusidic acid (8) but also to that obtained by conventional long-term intravenous antibiotic therapy combined with surgery (35). Co-trimoxazole can be used as a primary treatment (30 of 39 patients) or as a second-line treatment in cases of the failure of other previous standardized antibiotic regimens (9 of 39 patients). Our previous studies seemed to indicate a greater rate of success of long-term antibiotic therapy in the hip prosthesis group compared to that in the knee prosthesis group (4, 8, 9), and we therefore recommended for all patients with knee prosthesis infections administration of oral antibiotics for 6 months before and 3 months after one-stage removal and reimplantation of the prosthesis (regardless of whether the prosthesis was stable). In this study, knee prostheses were removed only when they were instable, and the success rate among these patients (62.5%) is similar to those that we found after use of our previous protocols. Our study demonstrates that orthopedic implant infections can be managed without removal of the foreign material, because 65.4% (17 of 26) of our cured patients could be treated with an antibiotic regimen alone. In these patients long-term oral antibiotic therapy alone may be a suitable alternative to classical medicosurgical treatment, especially when there are contraindications for surgery.

As for cost-effectiveness, a 6-month oral treatment of co-trimoxazole costs about $350, whereas a 1-day admission to the department of surgery costs about $700.

In conclusion, the results reported in this paper indicate that co-trimoxazole at high doses is efficient for long-term oral antibiotic therapy of multidrug-resistant *Staphylococcus*-infected orthopedic implants. Nevertheless, the presence of a relatively high number of side effects compared to those resulting from the use of other well-established oral protocols (e.g., fusidic acid plus rifampin or ofloxacin plus rifampin) suggests that co-trimoxazole should be prescribed only for the treatment of infections due to multidrug-resistant staphylococci, in which case therapy with other drugs will fail. For these indications, oral co-trimoxazole at high doses may be a valuable ambulatory alternative to parenteral glycopeptide therapy. The systematic removal or replacement of infected orthopedic material does not appear to be always necessary, but this issue must be reevaluated in further, larger studies.

ACKNOWLEDGMENTS

We thank Emma Birtles and Richard Birtles for critical review of the manuscript.

REFERENCES

1. **Brandt, C. M., W. W. Sistrunk, M. C. Duffy, A. D. Hanssen, J. M. Steckelberg, D. M. Ilstrup, and D. R. Osmon.** 1997. *Staphylococcus aureus* prosthetic joint infection treated with debridement and prosthesis retention. Clin. Infect. Dis. **24:**914–919.
2. **Brause, B. D.** 1989. Infected orthopedic prostheses, p. 111–127. *In* A. L. Bisno and F. A. Waldvogel (ed.), Infections associated with indwelling medical devices. American Society for Microbiology, Washington, D.C.
3. **Brause, B. D.** 1995. Infections with prostheses in bones and joints, p. 1051–1055. *In* G. L. Mandell, J. E. Bennett, and R. Dolin (ed.), Principles and practice of infectious diseases. Churchill Livingstone, New York, N.Y.
4. **Brouqui, P., M. C. Rousseau, A. Stein, M. Drancourt, and D. Raoult.** 1995. Treatment of *Pseudomonas aeruginosa*-infected orthopedic prostheses with ceftazidime-ciprofloxacin antibiotic combination. Antimicrob. Agents Chemother. **39:**2423–2425.
5. **Buchholz, H. W., R. A. Elson, and K. Heinert.** 1984. Antibiotic-loaded acrylic cement: current concepts. Clin. Orthop. **190:**96–108.
6. **Carsenti-Etesse, H.** 1991. Critères microbiologiques et pharmacologiques du choix des antibiotiques dans le traitement des infections ostéo-articulaires. Med. Mal. Infec. **21:**491–504.
7. **Craven, P. C.** 1993. Treating bone and joint infections with teicoplanin: hospitalization vs outpatient cost issues. Hosp. Formul. **28**(Suppl.)**:**41–45.
8. **Drancourt, M., A. Stein, J. N. Argenson, R. Roiron, P. Groulier, and D. Raoult.** 1997. Oral treatment of *Staphylococcus* spp. infected orthopaedic implants with fusidic acid or ofloxacin in combination with rifampicin. J. Antimicrob. Chemother. **39:**235–240.
9. **Drancourt, M., A. Stein, J. N. Argenson, A. Zannier, G. Curvale, and D. Raoult.** 1993. Oral rifampin plus ofloxacin for treatment of *Staphylococcus* infected orthopedic implants. Antimicrob. Agents Chemother. **37:**1214–1218.
10. **Eitel, F., A. Bauernfeind, and E. Lang.** 1997. Teicoplanin in the therapy of bone and joint infections. Curr. Ther. Res. **51:**97–109.
11. **Fitzgerald, R. H., and D. R. Jones.** 1985. Hip implant infection. Treatment with resection arthroplasty and late total hip arthroplasty. Am. J. Med. **78:**225–228.
12. **Fitzgerald, R. H., D. R. Nolan, D. M. Ilstrup, R. E. Van Scoy, J. A. Washington, and M. B. Coventry.** 1977. Deep wounds sepsis following total hip arthroplasty. J. Bone Joint Surg. Am. **59:**847–855.
13. **Gordin, F. M., G. L. Simon, C. B. Wofsy, and J. Mills.** 1984. Adverse reactions to trimethoprim-sulfamethoxazole in patients with acquired immunodeficiency syndrome. Ann. Intern. Med. **100:**495–499.
14. **Greenberg, R. N.** 1990. Treatment of bone, joint, and vascular-access-associated gram-positive bacterial infections with teicoplanin. Antimicrob. Agents Chemother. **12:**2392–2397.
15. **Gristina, A. G.** 1994. Implant failure and the immuno-incompetent fibro-inflammatory zone. Clin. Orthop. **298:**106–118.
16. **Grogan, T. J., F. Dorey, J. Rolling, and H. C. Amstutz.** 1986. Deep sepsis following total knee arthroplasty: ten-year experience at the University of California at Los Angeles Medical Center. J. Bone Joint Surg. Am. **68-A:** 226–234.
17. **Imman, R. D., K. V. Gallegos, B. D. Brause, P. B. Redecha, and C. L. Christian.** 1984. Clinical and microbiological features of prosthetic joint infection. Am. J. Med. **77:**47–53.
18. **Josefsson, C., and L. Kolmert.** 1993. Prophylaxis with systematic antibiotics versus gentamicin bone cement in total hip arthroplasty. Clin. Orthop. Related Res. **292:**210–214.
19. **Jupiter, J. B., A. W. Karchmer, J. D. Lowell, and W. H. Harris.** 1981. Total hip arthroplasty in the treatment of adult hips with current or quiescent sepsis. J. Bone Joint Surg. Am. **63-A:**194–200.
20. **Lettin, A. W. F., M. J. Neil, N. D. Citron, and A. August.** 1990. Excision arthroplasty for infected constrained total knee replacements. J. Bone Joint Surg. Am. **72-B:**220–224.
21. **Lew, D. P., and F. A. Waldvogel.** 1997. Osteomyelitis. N. Engl. J. Med. **336:**999–1007.
22. **Marotte, J. H., J. Servant, and P. Samuel.** 1991. Infections sur prothèse articulaire: indications respectives du remplacement de prothèse, de l'ablation du matériel sans repose et de de l'absence de geste chirurgical. Med. Mal. Infec. **21:**540–545.
23. **Masur, H.** 1995. Management of opportunistic infections associated with HIV infection, p. 1280–1294. *In* G. L. Mandell, J. E. Bennett, and R. Dolin (ed.), Principles and practice of infectious diseases. Churchill Livingstone, New York, N.Y.
24. **Michel, M., and L. Gutmann.** 1997. Methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci: therapeutic realities and possibilities. Lancet **349:**1901–1906.
25. **Norden, C. W.** 1991. Antibiotic prophylaxis in orthopedic surgery. Rev. Infect. Dis. **13:**842–846.

26. **Norden, C. W., and E. Keleti.** 1980. Treatment of experimental staphylococcal osteomyelitis with rifampin and trimethoprim, alone and in combination. Antimicrob. Agents Chemother. **17:**591–594.
27. **Norden, C. W., and M. Shaffer.** 1983. Treatment of experimental chronic osteomyelitis due to *Staphylococcus aureus* with vancomycin and rifampin. J. Infect. Dis. **147:**352–357.
28. **Salvati, E. A., R. P. Robinson, S. M. Zeno, B. L. Koslin, B. D. Brause, and P. D. Wilson.** 1982. Infection rates after 3175 total hip and total knee replacements performed with and without a horizontal unidirectional filtered air-flow system. J. Bone Joint Surg. Am. **64-A:**525–535.
29. **Sanzen, L., A. S. Carlsson, G. Josefsson, and L. T. Lindberg.** 1988. Revision operations on infected total hip arthroplasties. Two- to nine-year follow-up study. Clin. Orthop. **229:**165–172.
30. **Sattler, F. R., R. Cowan, D. M. Nielsen, and J. Ruskin.** 1988. Trimethoprim-sulfamethoxazole compared with pentamidine for treatment of *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. Ann. Intern. Med. **109:**280–287.
31. **Schutzer, S. F., and W. H. Harris.** 1988. Deep-wound infection after total hip replacement under contemporary aseptic conditions. J. Bone Joint Surg. Am. **70-A:**724–727.
32. **Shalit, I., S. A. Berger, A. Gorea, and H. Frimerman.** 1989. Widespread quinolone resistance among methicillin-resistant *Staphylococcus aureus* isolates in a general hospital. Antimicrob. Agents Chemother. **33:**593–594.
33. **Turnidge, J., and L. Grayson.** 1993. Optimum treatment of staphylococcal infections. Drugs **45:**353–366.
34. **Wharton, J. M., D. L. Coleman, C. B. Wofsy, J. M. Luce, W. Blumenfeld, W. K. Hadley, L. Ingram-Drake, P. A. Volberding, and P. C. Hopewell.** 1986. Trimethoprim-sulfamethoxazole or pentamidine for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. Ann. Intern. Med. **105:**37–44.
35. **Widmer, A. F., A. Gaechter, P. E. Oschner, and W. Zimmerli.** 1997. Antimicrobial treatment of orthopedic implant-related infections with rifampin combinations. Clin. Infect. Dis. **14:**1251–1253.
36. **Windsor, R. E., J. N. Insall, W. K. Urs, D. V. Miller, and B. D. Brause.** 1990. Two-stage reimplantation for the salvage of total knee arthroplasty complicated by infection. J. Bone Joint Surg. Am. **72-A:**272–278.
37. **Wroblewski, B. M.** 1986. One-stage revision of infected cemented total hip arthroplasty. Clin. Orthop. **211:**103–107.
38. **Zannier, A., M. Drancourt, J. P. Franceschi, J. M. Aubaniac, and D. Raoult.** 1991. Intérêt d'une technique de lyse cellulaire par choc thermique dans l'isolement des bactéries responsables d'infections ostéo-articulaires. Pathol. Biol. **39:**543–546.
39. **Zimmerli, W.** 1991. Rôle des antibiotiques dans les infections sur matériel étranger: modèle animal, tests microbiologiques et expériences cliniques. Med. Mal. Infec. **21:**529–534.
40. **Zinner, S. H., and K. H. Mayer.** 1995. Sulfonamides and trimethoprim, p. 354–364. *In* G. L. Mandell, J. E. Bennett, and R. Dolin (ed.), Principles and practice of infectious diseases. Churchill Livingstone, New York, N.Y.